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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,713	SCHENK, DALE B.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33;56-59,61 and 63-152* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,56-59,61 and 63-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response, including the two declarations under 37 CFR 1.132, filed on 10/19/05 have been entered. Claims 1-32, 34-55, 60, and 62 are canceled. Claims 33, 56-59, 61, and 63-152 are pending and under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Information Disclosure Statement

Applicant's supplemental IDS and proprietary IDS submitted on 10/19/05 have been considered and an initialed signed copy of the 1449 is attached to this office action.

Priority

The applicant has submitted an updated Application Data Sheet which identifies the instant application as a divisional of parent application 09/322,289, filed on 5/28/99. The applicant further states in their remarks that as amended the instant application has an effective filing date of 5/28/99.

The effective filing date of 5/28/99 as now claimed by the applicant is acknowledged. However, this applicant is required update the first page of the specification to reflect the amended continuity of this case as now claimed. The first paragraph of the specification was last

amended on 6/23/03. Please note as well that the current status of the 09/322,289 application should be included in any future amendment to the specification.

Claim Rejections - 35 USC 112

The rejection of claims 33, 56-59, 61 and 63-152 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as claimed, is **maintained.** Applicant's arguments and the declarations by Dr. Weiner and Dr. Jacobsen have been fully considered but have not been found persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the newly submitted declarations by Dr. Jacobsen and Dr. Weiner and accompanying evidence overcome the rejection of record and in particular the examiner's reliance on Bard et al. as showing that the 10D5 antibody does not have any effect on diseases associated with amyloid plaques comprising Aβ peptide by 1) providing evidence that the 10D5 antibody has beneficial effects on cognitive function and 2) providing evidence that an expert in gene therapy believes that undue experimentation would not be required to practice the "undemanding" form of gene therapy set forth in the instant methods as claimed.

The declaration of Dr. Jacobsen has been fully considered. The declaration provides the results from experiments conducted in a transgenic mouse model of Alzheimer's disease. 20 week old transgenic Tg2576 mice already exhibiting cognitive defects were administered a

single dose of either PBS or the 10D5 antibody by intraperitoneal injection and then subjected to the contextual fear conditioning assay 24 hours later which compares freezing behavior of the mice. The declaration presents results in which the mice treated with the 10D5 antibody showed a statistically significant improvement in contextual memory compared to the control mice. According to the declaration, these results show that the 10D5 antibody can have a beneficial effect on cognition and thus can be useful in treating Alzheimer's disease. In response, while the declaratory data provides evidence that the 10D5 antibody can have a treatment effect on existing cognitive defects in the transgenic mouse, the data does not refute the teachings of Bard that the 10D5 antibody does not have any beneficial effects on neuritic pathology. Further, like Bard et al., the experiments reported in the declaration are not analogous to the instant claims as they utilize the passive transfer of monoclonal antibody, not DNA encoding the heavy and light chains of the antibody. In addition, the experiment utilizes a single antibody, 10D5, and provides no evidence that any other antibody recognizing the same or a different epitope with Aβ 1–10 or Aβ 1–5 would yield the same results as the 10D5 antibody.

Turning to the Bard et al. reference, this post-filing reference was in fact submitted by the applicants as evidence for other antibodies that recognize an epitope within Aβ 1–10. The teachings of the Bard et al. reference were previously considered by the examiner. In the previous office action, it was noted that Bard et al. was published several years after the effective filing date of the instant application. The office action cited *In re Glass*, 181 USPQ 31, (CCPA 1974), for stating that if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the

practice of the invention. Instead, sufficiency must be judged as of the filing date. The applicant argues that MPEP states that the applicant can provide declaration after the filing date which demonstrates that the claimed invention works. This is agreed, however, for the reasons discussed in previous office actions and above, neither the Bard et al. reference nor the evidence provided in the Jacobsen declaration enable the claimed invention. The Bard et al. reference provides data concerning the ability of various monoclonal murine antibodies to bind or capture soluble Aβ, bind to Aβ present in plaque, and reduce neuritic dystrophy. As previously noted, Bard et al. is not analogous to the instant invention as Bard et al. teaches the direct administration of monoclonal antibody, not DNA encoding the heavy and light chains of the antibody. It is further noted that of the antibodies discussed in Bard, only the 10D5 antibody is disclosed by the applicant. The remaining antibodies are not disclosed in the specification, are not chimeric, humanized, or human as required by the claims, nor were they known in the prior art before the effective filing date. Furthermore, Bard et al. demonstrates that the treatment of disease characterized by amyloid plaques using monoclonal antibodies is unpredictable and affected by not only the isotype of the antibody, but by the affinity of the antibodies for Fc receptors on microglial cells rather than the affinity of the antibody for Aβ. Of the monoclonal antibodies tested by Bard et al., including the IgG1 antibody 10D5, Bard et al. shows that only two antibodies, both IgG2a isotype antibodies which recognized the 3-7 epitope of Aβ, were capable of providing neuronal protection and having any significant effect on neuritic dystrophy, following direct *in vivo* administration of the antibodies (see Bard et al., page 2027, Figure 4, particularly b and c, and column 2 paragraph 3). In fact, the 10D5 antibody disclosed in the specification did not reduce neuritic pathology (Bard et al., see the legend to Figure 4, page

2027). Thus, the Bard et al. reference in fact strengthens the position of the office as to the unpredictability of treating or preventing a disease characterized by amyloid plaques comprising Aβ peptide using any antibody which binds to an epitope within Aβ1-10. Further, in regards to the two IgG2a antibodies which were actually shown to have some effect after passive administration, it is noted that the specification fails to disclose these antibodies, or further fails to provide any guidance as to the effects of antibody isotype and affinity of the antibodies for Fc receptors on microglial cells on treatment efficacy. None of the teachings concerning antibodies that proved important as determined post-filing by Bard et al. are included in the specification as filed.

Thus, taken together, while the declaratory data shows that passive administration of 10D5 can beneficially affect cognition, Bard et al. shows that passive administration of 10D5 does not treat neuritic dystrophy. The claims as written are not limited to the treatment of cognitive dysfunction but rather read on the treatment of prophylaxis of any disease characterized by amyloid plaques comprising Aβ peptide. Thus, as the Jacobsen evidence only supports the treatment of cognitive dysfunction associated with Aβ peptide by the passive administration of the 10D5 antibody, it is not commensurate in scope with the claimed treatment. Further, and most importantly, neither Jacobsen nor Bard provide any guidance or data regarding the administration of nucleic acids encoding an antibody which is a clear requirement of the methods as claimed. The previous office actions have set forth in detail the reasons why passive administration of antibody is not analogous to the administration of DNA encoding the heavy and light chain of an antibody. The Jacobsen declaration does not address or overcome these grounds for rejection.

Regarding the declaration by Dr. Weiner, the statements of Dr. Weiner, an expert in the field of gene therapy, have been fully and respectfully considered. Dr. Weiner provides his opinion as an expert in the field that although there has been some "bad press" surrounding gene therapy, the number of clinical trials authorized by the FDA signal that gene therapy was regarded as sufficiently mature for human use by at least the mid 1990's, and thus prior the effective filing date of 1999 as now claimed by applicants. Dr. Weiner also states that in his opinion immunogenicity of vectors is not a particular problem, and that delivery of a DNA encoding a heavy and light chain could at least be expected to achieve transient expression of the antibody. Regarding the instant methods as claimed, Dr. Weiner further postulates that since the applicants Aβ peptide immunization experiments were therapeutic that a connection can be drawn between the those results and the instant claimed methods as both have the goal of generating antibodies to Aβ peptide in the blood. Finally, Dr. Weiner points to the Alvarerz et al. reference provided with the declaration which was published prior to the newly set forth effective filing date of 1999 that adenoviral vectors could be used to express therapeutic antibody in the blood.

In response, the relevance of the experiments employing the delivery of Aβ peptide to generate antibodies has been discussed in previous office and not found to be enabling as the Aβ peptide immunization generates polyclonal antibodies whereas following the methods of the instant claims would simply generate a single monoclonal antibody, and the specification does not sufficient guidance that any antibody selected from the genus of monoclonal antibodies that bind to an epitope of Aβ 1-10 or 1-5 would be capable of treating or preventing the breadth of diseases characterized by amyloid plaques comprising Aβ peptide. Regarding the Alvarez et al.

reference newly submitted with the declaration, Alvarez et al. does teach that an adenoviral vector can deliver nucleic acid encoding an antibody to cells *in vivo*. However, in Alvarez, the antibody is a single chain intracellular antibody, thus the protein produced does not leave the cell and is not expressed transiently or otherwise in the blood or any other tissue. As an intracellular antibody, the activity is limited to the cell which is transduced by the adenovirus. This is not analogous to the instant methods wherein the monoclonal antibody encoded by the claimed DNA is expected to be expressed extracellularly from a transfected cell such that it can travel to and bind Aβ peptide present in plaques in the brain or vascular system of patients with diseases characterized by amyloid plaques comprising Aβ peptide. The Alvarez et al. article does not demonstrate that it was either routine or predictable at the time of filing to administer a DNA encoding a secreted antibody to any site in a patient such that the secreted antibody would be capable of treating any disease or condition.

Further, while the statements of Dr. Weiner show that significant progress has been made in developing gene delivery systems and that the skilled artisan at the time of filing could at least expect some transient expression of an encoded gene following administration of DNA such as recombinant adenovirus or naked DNA, the statements of Dr. Weiner do not overcome the lack of enablement provided by the instant specification for treating or preventing Aβ peptide associated disease by administering any DNA encoding one of a genus of antibodies which bind Aβ 1-10 or Aβ 1-5 using any route of administration. The specification does not disclose any nucleic acid sequences for any antibody, nor does the specification provide any guidance as to the level of expression and duration of expression of any single monoclonal antibody from any cell transfected with a DNA according to the instant claims that correlates with a treatment or

prophylactic effect on any disease characterized by amyloid plaques such as Alzheimer's disease or amyloid angiopathy of the vascular or immune systems. Although the declaration by Dr. Weiner shows that the skilled artisan would not have needed undue experimentation to achieve *in vivo* gene delivery in 1999, there is nothing in the declaration to demonstrate that the skilled artisan would have found predictable the treatment of prevention of amyloid disease using gene therapy or that the skilled artisan would have been able to predict without undue experimentation which nucleic acids encoding a monoclonal antibody which binds to an epitope in Aβ 1–10 would be capable of treating or preventing any Aβ peptide associated disease.

As discussed in detail in the previous office actions, the rejection of record is clearly based upon the fact that the specification fails to provide the requisite teachings to enable the practice of the scope of the invention as claimed. The specification is primarily directed to immunization with Aβ peptides or with the passive transfer of monoclonal protein antibodies. The specifications teachings regarding the delivery of DNA encoding an antibody which binds to an epitope within Aβ1-10 are limited to a brief and general description of gene transfer and vectors on page 25 of the specification and are entirely prophetic. The specification provides no specific guidance as to particular vectors which are in fact capable of expressing sufficient levels of any encoded antibody over multiple administrations resulting in treatment of diseases such as Alzheimer's disease. Based on the combined teachings of Marshall et al., Eck et al., Verma et al., and Orkin et al., it is clear that more is required to predict therapeutic success. Furthermore, the specification provides no guidance as to any nucleic acid sequences encoding any antibody which binds to an epitope within Aβ1-10 or within Aβ1-5 whose expression in the blood or any other location in the body at any level or duration or expression would be sufficient to reduce or

prevent amyloid plaques or plaque formation. The closest evidence provided by the specification concerns the passive administration of protein antibodies. However, this evidence of record demonstrates further complicates the issue since the evidence demonstrates that even with direct administration of protein antibody which binds to an epitope within Aβ1-10, therapeutic efficacy is not predictable. Example XI shows that administration of the 2H3 antibody directed against an epitope within Aβ1-12 was ineffective in preventing or ameliorating plaque deposits in transgenic mice due to problems with rapid antibody clearance. Further, as discussed in detail above, the Bard et al. reference provided by the applicants clearly demonstrates that unpredictability of actually treating neuritic pathology when administering monoclonal antibodies which actually bind to Aβ peptide in plaques and even have some efficacy in reducing Aβ peptide concentrations *in vivo*. Thus, the evidence or record shows that even following direct protein antibody administration, the treatment of disease associated with amyloid plaques with antibodies that bind to an epitope within Aβ1-10 is not predictable. Therefore, based on the art-recognized unpredictability of achieving therapeutic levels of gene expression using currently available vectors at the time of filing, based on the unpredictability in treating or preventing diseases associated with amyloid plaques comprising Aβ peptide using any monoclonal antibody that binds to an epitope within Aβ1-10 as evidenced by the specification and the Bard et al. reference, the limitation of the applicant's working examples to the administration of protein antibody and not nucleic acid encoding an antibody, the lack of specific guidance as to vectors, promoters, routes of vector administration, or nucleic acid sequences encoding antibodies which are capable of treating or preventing diseases associated with amyloid plaque formation, or specifically Alzheimer's disease, and the breadth of the claims, it would have required undue

experimentation to practice the instant invention as claimed. Thus, the evidence provided, including the declarations by Drs. Koller, Jacobsen, and Weiner, the references by Bard et al, Arafat et al., and Alvarez et al., does not overcome the lack of enabling disclosure in the specification for the claims as written.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official

communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER